

Review article

Microglia, neurodegeneration and loss of neuroendocrine control

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ABSTRACT

Microglia, the primary regulators of inflammatory responses in the brain, suffer deterioration during aging culminating in their inability to generate adequate adaptive responses to maintain physiological homeostasis in brain tissue. Microglia affect the function of other glial cells and neurons, including those involved in the hypothalamic control of body homeostasis. Microglial dysfunction with aging in cognitive areas such as the hippocampus is known to associate with cognitive decline; more recently, microglial alterations in the hypothalamus during midlife was suggested to participate in changes in the endocrine and metabolic control exerted by this brain region. Consequently, the feed-back loops between endocrine glands and the hypothalamus are altered. This generates a vicious circle in which the plasma levels of key neuroprotective hormones, such as gonadal hormones, insulin-like growth factor-1, growth hormone and leptin and their hypothalamic signaling are decreased, which further enhances microglial alterations and deterioration of hypothalamic function. Hypothalamic dysfunction is a risk factor for neurodegenerative diseases and these diseases in turn promote additional alterations in hypothalamic microglial cells, which are unable to cope with the neurodegenerative process, resulting in permanent damage of the neuronal-glial circuits controlling endocrine homeostasis, food intake and body metabolism. Thus, a “vicious cycle” may such be initiated.

1. Introduction

Health, wellbeing and homeostasis of the human body are highly dependent on the correct functioning of the hypothalamus. This key brain center exerts its homeostatic control through two parallel and complementary mechanisms: 1) The release of hypothalamic neuropeptides that control the release of hormones that modify the activity of peripheral endocrine glands. 2) The governance of hypothalamic and extra-hypothalamic neuronal circuits involved in endocrine functions, food intake and energy balance through the release of neurotransmitters and the modulation of neurotransmission. The activity of hypothalamic neuronal circuits controlling body homeostasis is under fine temporal tuning by peripheral hormones and vagal inputs that send feed-back regulatory signals to the hypothalamus, assuring that hypothalamic activity is adequately adjusted to body needs. The neuronal circuits that regulate body homeostasis have been actively studied for many years and our understanding of this central control has progressively increased. It is assumed that defective functioning of these circuits underlies the decline in neuroendocrine systems associated with

aging and neurodegenerative conditions (Zhang et al., 2013). A major question remains as to why these circuits become dysfunctional under these circumstances. The answer may reside in a cellular component that is emerging as a key player in the hypothalamic neuroendocrine regulation: glial cells (Chowen et al., 2016; Douglass et al., 2017b; Ojeda et al., 2008; Oliet et al., 2004).

In the mammalian brain, glial cells are classified as microglia and macroglia (Fig. 1). Microglia, the macrophages of the brain, actively and continuously sense for alterations in the homeostatic conditions of brain tissue. They have phagocytic activity and are the primary regulators of local inflammatory responses in the neural parenchyma (neuroinflammation) in response to disturbances in the cellular environment (Michell-Robinson et al., 2015). Macroglia are composed of a variety of cell types, including astrocytes, oligodendrocytes and NG2 cells, a more recently recognized type of glial cell characterized by the expression of NG2 proteoglycan (Hill and Nishiyama, 2014), as well as specialized macroglia located in the cerebellum (Bergmann glia) and the hypothalamus (tanycytes). This broad variety of glial cell types in the mammalian brain is not found in invertebrates or lower vertebrates.

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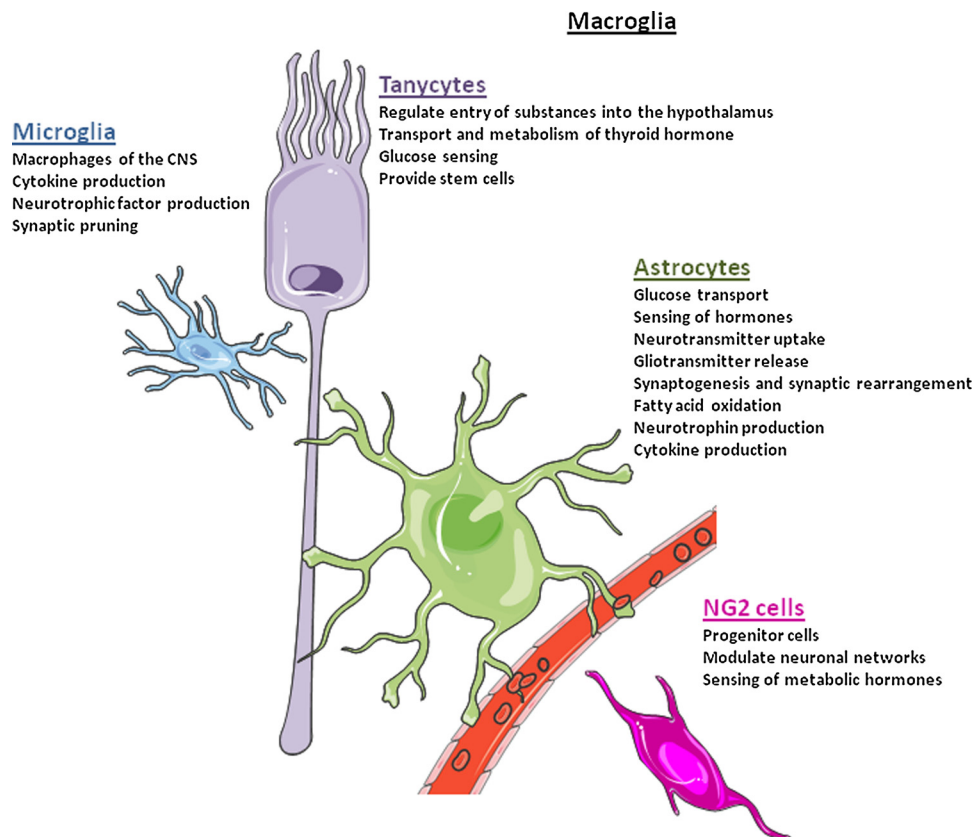


Fig. 1. Role of hypothalamic glial cells in neuroendocrine control. Tanycytes, microglia, astrocytes and NG2 cells participate in the sensing of endocrine and metabolic signals and regulate the function and activity of the hypothalamic neuroendocrine neuronal circuits.

Indeed, it appears that glial cells have experienced more morphological and functional changes throughout phylogenetic evolution than neurons. This must attest to their increasing importance throughout evolution and in higher species.

Glial cells were originally considered to be mere elements of support for neurons; however, we now know that they perform a wide spectrum of actions that are essential in the regulation of brain function. Astrocytes are sensitive to changes in neuronal activity through their expression of receptors for neurotransmitters and neuromodulators and they actively participate in the processing of information in the brain. Indeed, they regulate neuronal communication by releasing gliotransmitters, such as ATP, glutamate, GABA and D-serine. They also form cellular syncytia connected by gap junctions that function to intercommunicate the synaptic activity of distant neurons. Thus, in conjunction with pre- and postsynaptic neuronal terminals, astrocyte processes are now recognized as the third component of synapses (Papouin et al., 2017; Perea et al., 2009).

Astrocytes also play a key role in brain function by providing fuel to sustain neuronal function, adapting the energy supply to neuronal activity (Belanger et al., 2011). Astrocytes and other macroglial cells, such as tanycytes, transport glucose from the circulation, participate in glucose-sensing mechanisms (Elizondo-Vega et al., 2015; Frayling et al., 2011), accumulate energy deposits in the form of glycogen (Dringen and Hamprecht, 1992) and sense neuronal activity in order to provide lactate to neurons according to their metabolic needs (Belanger et al., 2011). Astrocytes, together with tanycytes, endothelial cells and pericytes, are an essential component of the blood-brain barrier and regulate the flux of molecules between the body and the brain (Cabezas et al., 2014). Moreover, astrocyte end-feet surrounding brain capillaries are fundamental in synchronizing neuronal metabolism with cerebral blood flow (Petzold et al., 2008; Takano et al., 2006). In the hypothalamus, morphological changes in astrocytes and tanycytes are

associated with modifications in the synaptic plasticity of neuronal circuits involved in regulating the release of hormones, such as gonadotropin-releasing hormone (GnRH) and oxytocin (Chowen et al., 2016; Olié et al., 2008; Sharif et al., 2013). Astrocytes and tanycytes also release factors that regulate the activity of hypothalamic neurons, including transforming growth factor (TGF) α , TGF β 1, TGF β 2, fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor A (VEGF-A), prostaglandins and progesterone (Langlet et al., 2013; Prevot et al., 2003; Sinchak et al., 2003).

Hypothalamic glial cells are also involved in the control of food intake and energy expenditure. Energy metabolism is primarily regulated by two groups of neurons in the human hypothalamic infundibular nucleus (arcuate nucleus in rodents): 1) Pro-opiomelanocortin (POMC) neurons that release α -melanocyte stimulating hormone (α -MSH) to promote energy expenditure and inhibit feeding and 2) Neuropeptide Y (NPY) neurons that release Agouti-related peptide (AgRP) and NPY to stimulate feeding and decrease energy expenditure (Koch and Horvath, 2014; Luquet et al., 2005). Both POMC and NPY neurons are under the control of systemic feed-back signals including the anorexigenic hormone leptin, produced mainly by adipocytes, and the orexigenic hormone ghrelin produced in the stomach, with these neurons projecting to and regulating other neuronal populations involved in metabolic control. Astrocytes, microglia, NG2-glia and tanycytes participate in the hypothalamic sensing of metabolic hormones, such as insulin and leptin (Djogo et al., 2016; Fuente-Martin et al., 2012; Garcia-Caceres et al., 2016; Kim et al., 2014; Wang et al., 2015) and other metabolic signals, such as glucose and fatty acids (Belanger et al., 2011; Elizondo-Vega et al., 2015; Le Foll et al., 2014) (Fig. 1). For instance, hypothalamic astrocytes express receptors for and respond to metabolic hormones, including insulin, leptin, ghrelin, estradiol and glucocorticoids (Chowen et al., 2016; Diano et al., 1998a; Douglass et al., 2017b; Fuente-Martin et al., 2016; Garcia-Caceres et al., 2016;

Hsueh et al., 2009). Expression of leptin receptors in astrocytes and NG2 cells is necessary for the correct actions of leptin on metabolic circuits in the hypothalamus (Djogo et al., 2016; Kim et al., 2014; Wang et al., 2015). The genetically induced lack of leptin receptors in glial fibrillary acidic protein (GFAP) positive astrocytes modifies the morphological interaction of the cellular processes of these glial cells with the surface of POMC and AgRP neuronal somas. This is associated with alteration of the number of synaptic inputs to these neurons, as well as the balance between stimulatory and inhibitory inputs, and thus modifications in their activity (Kim et al., 2014). Leptin also controls the transport of glucose and glutamate by astrocytes, affecting their regulation of neuronal metabolism (Fuente-Martín et al., 2012). Moreover, astrocytes are fundamental in mediating the effects of insulin on neuronal metabolism throughout the brain and in the hypothalamus this affects systemic energy homeostasis (Fernandez et al., 2017; García-Caceres et al., 2016).

Tanycytes, which sense, transport and respond to metabolic signals such as glucose, leptin, IGF-1 and estradiol, also metabolize thyroxine (T4) to triiodothyronine (T3) and are therefore important mediators of the actions of thyroid hormone in the hypothalamus (Balland et al., 2014; Diano et al., 1998b; Elizondo-Vega et al., 2015; Frayling et al., 2011; Langlet et al., 2013). Glia, and in particular tanycytes, are a source of neuroprogenitor cells (Chaker et al., 2016; Lee et al., 2012), allowing the renovation of hypothalamic neuroendocrine and metabolic circuits and their continual adjustment to the nutritional/hormonal environment (Lee et al., 2012; McNay et al., 2012).

The surge of publications in the past decade analyzing glial cells in metabolic homeostatic control is due, at least in part, to the demonstration that in high fat diet (HFD)-induced obese rodents inflammatory processes in the hypothalamus are directly involved in central insulin resistance and disruption of systemic glucose homeostasis (De Souza et al., 2005) and that hypothalamic inflammation has also been observed in humans with obesity (Thaler et al., 2012). Microglia have been closely linked to the obesity-induced inflammation in the hypothalamus, with these glial cells shown to respond to both hormonal and nutrient signals to initiate inflammatory signaling (Gao et al., 2014; Milanski et al., 2009; Valdearcos et al., 2014). Depletion of microglia in the medial basal hypothalamus or inhibition of inflammatory signaling cascades specifically in microglia improves the metabolic profile in obese subjects with insulin resistance (Andre et al., 2017; Valdearcos et al., 2017, 2014), with a similar observation being reported in astrocytes (Buckman et al., 2015; Douglass et al., 2017a). However, the process of astrogliosis is biphasic (Thaler et al., 2012), with a rapid initial phase interpreted as protective and involved in the physiological adaptation to increased energy intake (Buckman et al., 2015), while delayed prolonged astrogliosis participates in the detrimental response to obesity/poor nutrition, including secondary complications and perpetuation of increased weight gain (Douglass et al., 2017a).

As will be seen in the following sections, we propose that understanding the role of glial cells in neuroendocrine and metabolic control is key for delineating how hypothalamic dysfunction participates in aging and neurodegeneration, as well as how poor nutrition and obesity influence these processes and the mechanisms involved. Indeed, both aging and neurodegeneration are characterized by alterations in glial cell function and this occurs in parallel with enhanced neuroinflammation in the hypothalamus.

2. Age-associated hypothalamic dysfunction during midlife is linked to microglial alterations

2.1. Aging of endocrine systems

Throughout life there is continuous crosstalk between the endocrine glands and the hypothalamus to control and adjust physiological processes to maintain homeostasis. This occurs through specific feed-back loops that must be under constant adjustment in order to adapt to

changes in the environment. There are certain physiological periods and events in the life of an individual when these adjustments are quite complex, such as during early development, puberty, reproductive cycles, pregnancy, parturition, the early postpartum period and lactation (García-Segura, 2009). The feed-back loops between the hypothalamus and endocrine glands also undergo striking reorganization during aging and under pathological conditions (García-Segura, 2009). The aging process is gradual, but with clear alterations in endocrine gland and hypothalamic function becoming apparent around midlife and this is associated with a decline in the levels of many circulating hormones (Lamberts et al., 1997). Since the hypothalamus controls the activity of the endocrine glands and the hormones produced by these glands feed-back to regulate hypothalamic function, it has been difficult to determine whether the midlife-appearance of endocrine dysfunction initiates in the hypothalamus or if it is triggered by alterations in peripheral hormone levels. One likely scenario is that during aging there is continuous and progressive remodeling of the feed-back loops in order to maintain the coordinated actions of the hypothalamus and endocrine glands, but this eventually culminates in a catastrophic point at which these regulatory feed-back loops cannot be sufficiently adjusted to maintain systemic homeostasis. They thus become permanently impaired, accelerating and perpetuating the decline in hypothalamic function.

2.2. Microglia senescence

Brain aging is associated with microglial senescence, which results in increased gliosis and neuroinflammation (Cornejo and von Bernhardi, 2016; Matt and Johnson, 2016). It should be made clear that senescent microglia do not have the same phenotype as microglia that have been activated in response to acute brain injury or infection. Young reactive microglia exert neuroprotective actions to promote tissue repair and the recovery of tissue homeostasis. In contrast, senescent microglia are dysfunctional cells that are unable to properly react to brain alterations (Fig. 2). Senescent microglia exhibit increased basal phagocytic activity, but their induced phagocytic activity is impaired. Their dendritic arborization is decreased, as is their motility and capacity to shift from a proinflammatory to an anti-inflammatory phenotype (Cornejo and von Bernhardi, 2016; Matt and Johnson, 2016). These changes in aged microglia have an important impact on brain function. The decreased dendritic arborization and motility of aged microglia reduces their surveying capacity and their ability to react to harmful stimuli, which in turn hinders their effectiveness in adequately maintaining homeostasis in brain tissue. Furthermore, microglial phagocytic activity is essential for synaptic plasticity and adult neurogenesis to occur correctly (Schafer et al., 2012; Sierra et al., 2010) and, as senescent microglia are incapable of adequately adapting phagocytosis to homeostatic needs, these functions are compromised in the aging brain. Senescent microglia are also unable to adjust their transition between pro-inflammatory and anti-inflammatory activity to meet homeostatic needs resulting in the inadequate release of pro-inflammatory cytokines, such as interleukin (IL) -1 β , IL-6 and tumor necrosis factor (TNF)- α . This promotes chronic neuroinflammation and alters the function of other brain cell types, including astrocytes and neurons (Cornejo and von Bernhardi, 2016; Matt and Johnson, 2016; Zhang et al., 2013). Alteration of these cell types in the hypothalamus would directly affect neuroendocrine and endocrine function, including metabolic control.

2.3. Hypothalamic inflammation and aging

It has been suggested that, at least in mice, aging of the hypothalamus is the cause of systemic aging (Zhang et al., 2013). Although the existence of senescent microglia has not been demonstrated in the hypothalamus, microglial cells in this brain region progressively acquire a dysfunctional proinflammatory phenotype during the aging process

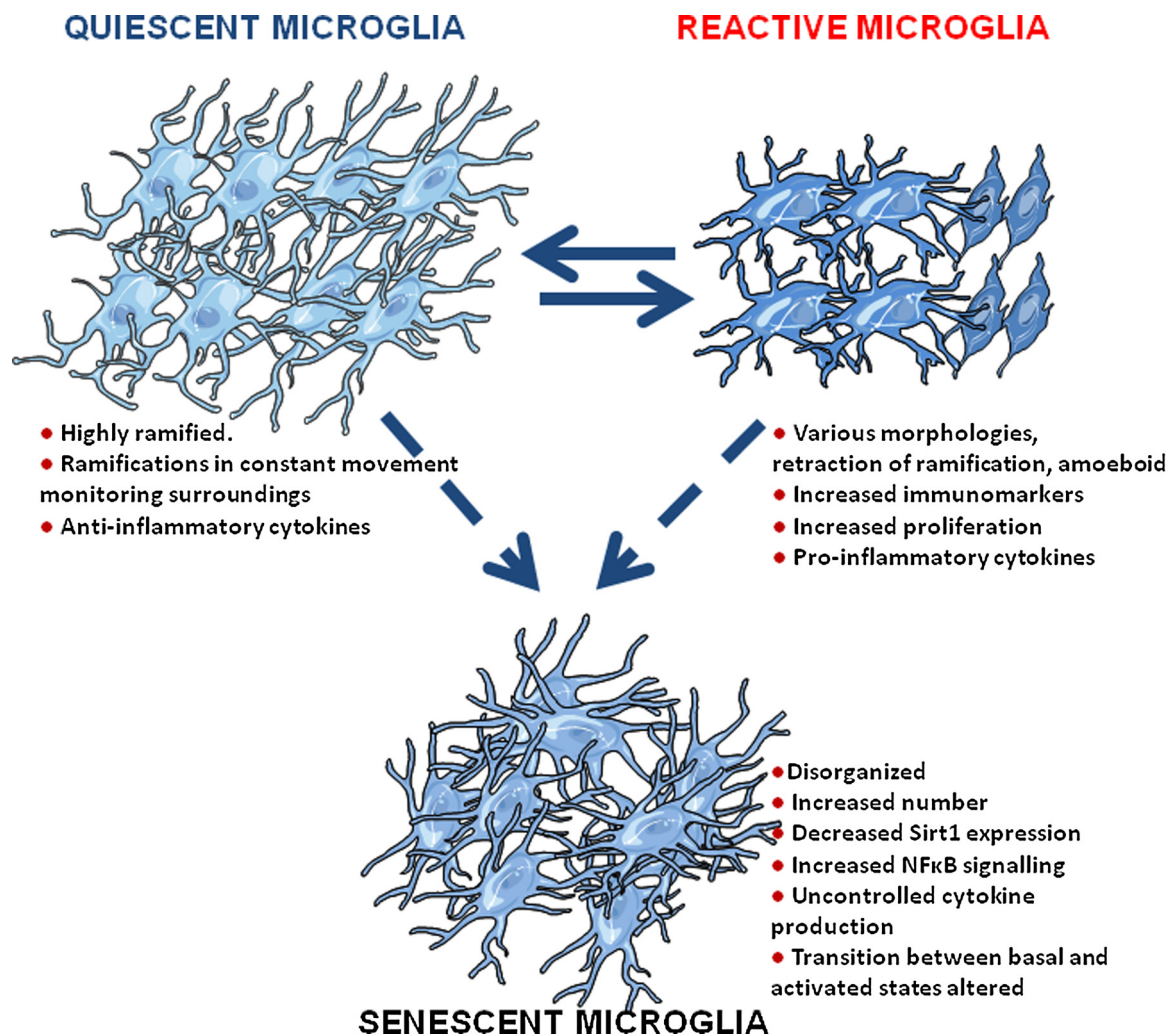


Fig. 2. Characteristics of senescent microglia. Representation of the differences between quiescent, activated and senescent microglia. In contrast to young activated microglia, senescent microglia are unable to mount an adequate homeostatic inflammatory response.

that is characterized by elevated nuclear factor κ – light chain – enhancer of activated B cells (NF κ B) signaling (Zhang et al., 2013). The inappropriate activation of NF κ B in hypothalamic microglia and the resulting increased expression and release of pro-inflammatory cytokines, such as TNF- α , activates NF κ B in neurons (Zhang et al., 2013). This proinflammatory condition is associated with increased expression of TGF β in astrocytes, which results in further hypothalamic NF κ B activation (Yan et al., 2014). Therefore, in the aged hypothalamus, astrocytes acquire a reactive phenotype that involves changes in cell morphology and the release of glial factors that alter neuron-glia crosstalk (Kaur et al., 2008; Yan et al., 2014). Since astrocytes regulate the actions of peripheral hormones on hypothalamic neurons, the alteration in their function, as a consequence of the local uncontrolled neuroinflammatory environment, will in turn affect the hypothalamic regulation of body homeostasis. Indeed, not only are the circuits controlling systemic metabolism altered, resulting in an increased propensity to gain weight and develop diseases such as diabetes mellitus type 2, but inflammatory processes in the hypothalamus of aged mice result in the down-regulation of GnRH expression, which contributes to systemic aging (Zhang et al., 2013). These findings in mice suggest that age-associated microglial alterations in the hypothalamus, and the consequent over-activity of NF κ B signaling in microglia and astrocytes, is involved in systemic aging.

Deregulation of the hypothalamic neuroinflammatory response during aging results in modifications in the control of neuroendocrine

axes that in turn amplify the process of hypothalamic aging (García-San Frutos et al., 2012; Yan et al., 2014; Zhang et al., 2013) (Fig. 3). For instance, the down-regulation of GnRH secretion by hypothalamic inflammation (Morelli et al., 2014; Zhang et al., 2013) affects the hypothalamic control of gonadal hormone synthesis. In mammals, gonadal hormones are essential signals for the modification and reorganization of neurons, glial cells and their interactions that occur in the hypothalamus and other brain regions during critical periods of life such as prenatal development, puberty, reproductive cycles, pregnancy, motherhood, menopause and aging (García-Segura, 2009). Plasma levels of gonadal hormones, as well as their precursor dehydroepiandrosterone (DHEA), decrease in both men and women during midlife (Lamberts et al., 1997). These hormones exert neuroprotective actions and reduce the activation of astrocytes and microglia, thus decreasing gliosis and neuroinflammation (Acáz-Fonseca et al., 2016). Hence, it is plausible that the decline in gonadal hormone levels during midlife in men and women is one of the main phenomena promoting hypothalamic aging. The age-associated decrease in gonadal hormones is accompanied by reduced levels of growth hormone (GH), which in turn results in decreased serum levels of IGF-1 (Lamberts et al., 1997), a component of the GH axis, whose expression and signaling in different tissues, including the brain, is regulated by estradiol (Cardona-Gomez et al., 2002; Munive et al., 2016; Perianes-Cachero et al., 2015; Sohrabji, 2015). IGF-1 is a neuroprotective factor that promotes neuron survival and adult neurogenesis, including hypothalamic neurogenesis

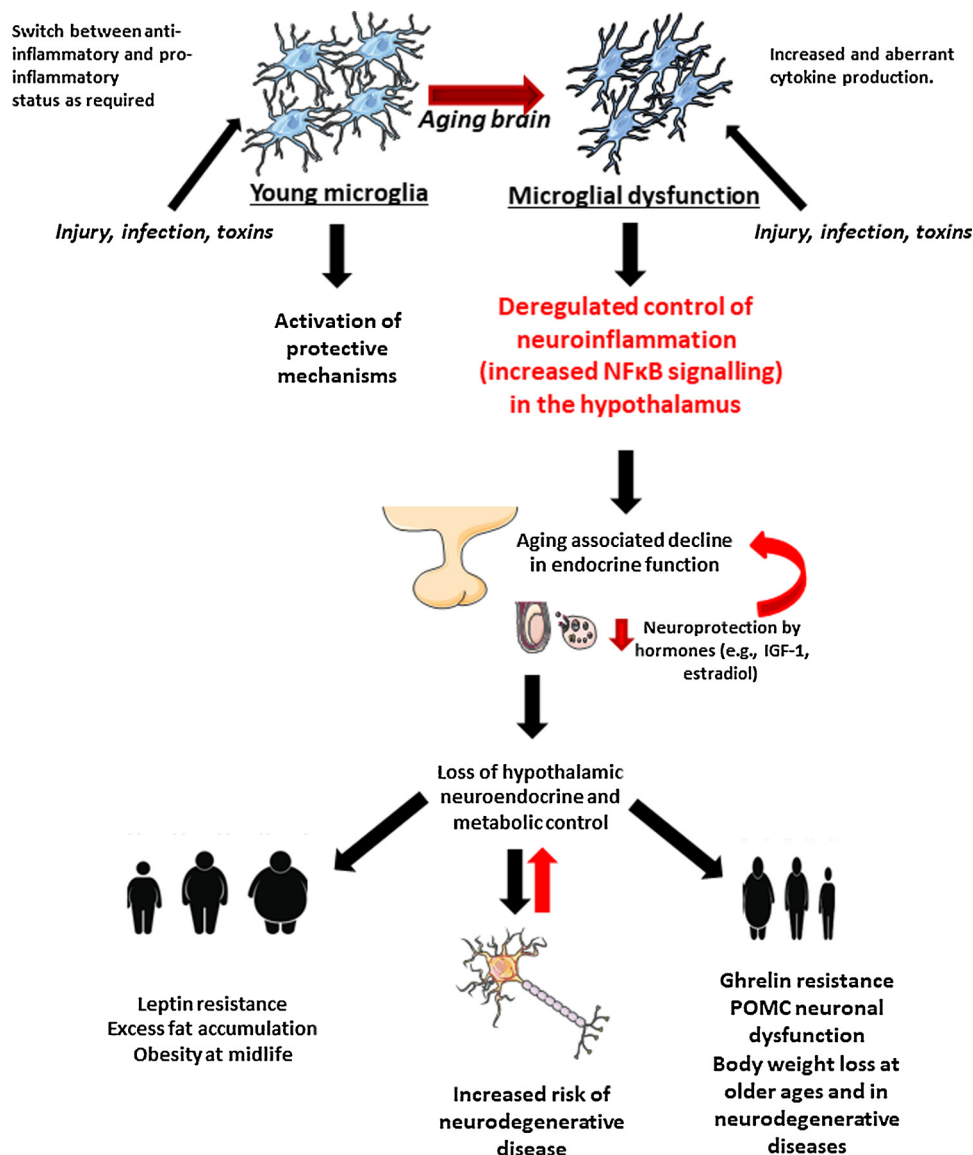


Fig. 3. Vicious circle of aging-associated hypothalamic neuroinflammation and loss of metabolic control. Microglia at midlife causes hypothalamic inflammation and the impaired function of hypothalamic neuroglial regulation of metabolic control. This causes metabolic alterations that are exacerbated by poor dietary habits, which promote hypothalamic microglia activation and further hypothalamic inflammation, enhancing the loss of neuroendocrine and metabolic control.

(Chaker et al., 2016; Perez-Martin et al., 2010), and reduces gliosis and neuroinflammation, down-regulating NFκB activity (Bellini et al., 2011). Although the brain also produces IGF-1, circulating IGF-1 has been shown to directly affect brain function (Carro et al., 2005; Trejo et al., 2007); thus, the midlife decline in circulating levels of this hormone could further enhance hypothalamic aging. In addition, the IGF-1 receptor interacts with estrogen receptor alpha in the hypothalamus to activate neuroprotective and anti-inflammatory signaling mechanisms (Mendez et al., 2003) and the age associated decline in the levels of gonadal hormones and IGF-1 could impair this interaction. This is not only pertinent regarding the decrease in circulating estradiol levels in midlife women, as in fact, peripheral testosterone is converted to estradiol within the human male and female brain. Therefore, the age-associated decline in plasma testosterone levels in men and the age-associated decrease in plasma levels of estradiol in women, together with the decrease in plasma IGF-1 levels in both sexes (Lamberts et al., 1997), reduces the coordinated neuroprotective and anti-inflammatory signaling of estrogen receptor alpha and the IGF-1 receptor in the brain, resulting in enhanced hypothalamic gliosis and neuroinflammation.

Thus, the parallel decline in the activity of the GH and gonadal hormone axes may be one of the main events initiating generalized hypothalamic dysfunction with aging. The physiological differences between the sexes, especially regarding the reproductive axis and steroid hormone production, varyingly affect this aging process and the associated peripheral outcomes. Indeed, females tend to be less susceptible to metabolic alterations, at least before menopause (Palmer and Clegg, 2015).

3. Microglia are involved in the alteration of neuroendocrine control at midlife, which further exacerbates hypothalamic dysfunction

3.1. Aging, dietary habits and hypothalamic inflammation

The age-associated increase in hypothalamic inflammation causes impaired hypothalamic sensing of metabolic hormones and the inadequate regulation of energy expenditure, which in turn promotes increased adiposity in men and women during midlife. These metabolic

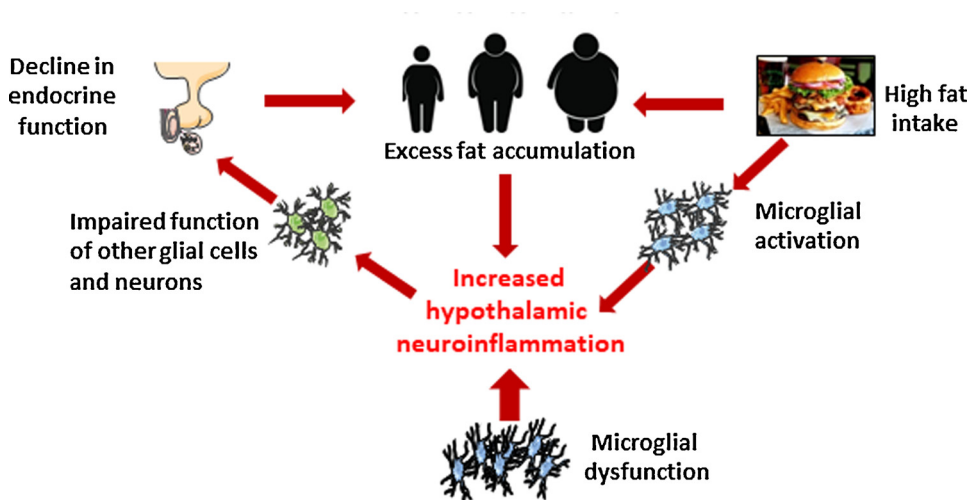


Fig. 4. Role of microglia on the loss of neuroendocrine control by the hypothalamus. Impaired function of microglia in the aged brain results in aberrant NF κ B activation in the hypothalamus, affecting the function of neurons and other glial cells. This results in loss of neuroendocrine and metabolic control. The consequent decrease in the levels of neuroprotective hormones, such as IGF-1 and estradiol, further exacerbates hypothalamic dysfunction. Neurodegenerative diseases affect the hypothalamus and further enhance endocrine and metabolic alterations.

alterations caused by hypothalamic aging can be exacerbated by life-style factors, such as diets rich in fat and sugar and sedentary behavior, which enhance hypothalamic inflammation (Milanski et al., 2009; Thaler et al., 2012) and impair hypothalamic control of metabolic function; this can result in obesity and metabolic syndrome (Fig. 4). In addition, obesity associated hypothalamic inflammation impairs GnRH secretion (Morelli et al., 2014), which as previously stated contributes to systemic aging (Zhang et al., 2013).

Peripheral metabolic alterations associated with obesity and poor dietary habits, such as high levels of dietary saturated fatty acids, activate NF κ B signaling in mediobasal hypothalamic microglia, promoting autophagy, endoplasmic reticulum stress and oxidative stress, resulting in hypothalamic insulin, ghrelin and leptin resistance and further promoting hypothalamic neuroinflammation and dysfunction (Kleinridders et al., 2009; Milanski et al., 2009; Valdearcos et al., 2014; Zhang et al., 2008). High fat diet intake stimulates neurogenesis in the hypothalamus, with this increase in cell turnover thought to be beneficial by promoting metabolic adaption to dietary changes (Lee et al., 2012; McNay et al., 2012). However, hypothalamic neurogenesis and the generation of neurons involved in metabolic control decrease with age (Chaker et al., 2016; McNay et al., 2012), which reduces this adaptive capacity and results in increased weight gain in response to dietary challenges. This decrease in proliferative capacity may be at least partially due to the age associated increase in local inflammatory processes initiated by microglia and the impaired neurogenesis-associated phagocytic function of microglia, in conjunction with the decline in hypothalamic neurogenesis promoting hormones such as IGF-1 and estrogens (Chaker et al., 2016; Lamberts et al., 1997; Sierra et al., 2010).

3.2. Microglia, diet and hypothalamic inflammation

The deletion or silencing of microglia in the mediobasal hypothalamus of rodents prevents saturated fatty acid-induced hypothalamic neuroinflammation and high fat diet - induced weight gain (Andre et al., 2017; Valdearcos et al., 2017, 2014). Thus, we could propose the following scenario: saturated fatty acids from the acute ingestion of a high fat diet induce the transient release of proinflammatory molecules by microglia, initially as an adaptive response to maintain metabolic control (Thaler et al., 2012). However, if the high fat diet is prolonged, the adaptive response of microglia is impaired, resulting in chronic neuroinflammation and hormonal changes that perpetuate weight gain and neuroinflammation (Gao et al., 2014; Thaler et al., 2012). Similar to microglia during aging, diet-induced reactive microglia would activate astrocytes, altering their morphology and their contacts with neurons and brain capillaries (Horvath et al., 2010). This alteration of

astrocytes, and possibly tanycytes, would affect the transport of leptin and other metabolic signals through the blood-brain barrier (Balland et al., 2014; Fuente-Martín et al., 2016, 2012), promoting decreased hypothalamic leptin sensing and impaired insulin signaling. Central insulin and leptin resistance impair the correct functioning of hypothalamic circuits controlling food intake and metabolism (Halaas et al., 1997; Sears and Perry, 2015), further promoting obesity and resulting in a vicious circle. Thus, obesity and aging trigger similar pathophysiological mechanisms associated with increased hypothalamic microglia dysfunction and deregulated neuroinflammatory control.

3.3. Aging, microglia and metabolism

Age-associated impairment of the hypothalamic control of systemic metabolism can result in obesity during midlife, but prolonged hypothalamic microglial dysfunction, which is enhanced by obesity, is associated with anorexia at older ages (Fig. 3). During midlife, increased body weight is, at least in part, the consequence of obesity-associated leptin and insulin resistance (Kleinridders et al., 2009; Purkayastha et al., 2011; Spielman et al., 2014) and the impaired functioning of NPY neurons caused by inflammation and deregulated microglial activation (Dalvi et al., 2017). Permanent microglial activation could in addition contribute to both the age-associated death of hypothalamic neurons (Leite et al., 2016) and the age-associated decrease in hypothalamic neurogenesis, which is then unable to replace the damaged neurons. This would cause enhanced and progressive functional impairment of hypothalamic circuits in elderly people, including those circuits involved in metabolic control. Moreover, at older ages the effect of ghrelin resistance in AgRP/NPY neurons predominates (Briggs et al., 2014; Miyazaki et al., 2014), and together with the stimulation of POMC neurons by hypothalamic cytokines (Jang et al., 2010; Shi et al., 2013) increased energy expenditure and decreased appetite would be favored. Aging is associated with a decline in plasma ghrelin levels and a decrease in the acylated (active)/desacylated ghrelin ratio in humans, which is thought to be involved in the decreased appetite observed in the elderly (Nass et al., 2014; Rigamonti et al., 2002). The decrease in hypothalamic ghrelin signaling further contributes to increased microglia activation (Fujitsuka et al., 2016), enhancing hypothalamic neuroinflammation and the deterioration of hypothalamic metabolic control. Therefore, in addition to the alterations in ghrelin signaling in hypothalamic AgRP/NPY neurons with aging, microglial activation and cytokine production in the hypothalamus can contribute to weight loss in the elderly or cachexia in disease by stimulating POMC neurons (Jang et al., 2010; Shi et al., 2013).

Ghrelin also regulates systemic metabolism by acting on

extrahypothalamic regions, such as the ventral tegmental area and actions of ghrelin on the dopaminergic neurons of this brain region are involved in the regulation of reward and motivation (Stievenard et al., 2017). Thus, altered ghrelin signaling in the aged brain could also alter motivation for food, contributing to weight loss and physical frailty in elderly individuals and in patients with neurodegenerative diseases.

Aging in humans is characterized by elevated plasma levels of interleukin (IL)-1 β , IL-6, TNF α and leukemia inhibitory factor (LIF) (Gameiro et al., 2010; Maggio et al., 2005). These cytokines reach the brain where they stimulate the inflammatory response of hypothalamic microglia. Under neuroinflammatory conditions, glial cells in the hypothalamic arcuate nucleus of rodents modify their physical interaction with the surface of POMC neurons, changing the ratio of excitatory and inhibitory synaptic inputs on these neurons and increasing their activity (Horvath et al., 2010). In addition, the activation of NF κ B promotes POMC transcription (Jang et al., 2010; Shi et al., 2013). The increased activity of POMC neurons then results in anorexia, which can be reversed with antagonists of NF κ B (Jin et al., 2016). Moreover, studies of genetically modified rodents have shown that hypothalamic IL-1 β and LIF stimulate the production of α -MSH through a mechanism involving NF κ B activation in POMC neurons (Grossberg et al., 2010). This scenario would result in suppression of food intake and enhanced energy expenditure.

Physical frailty is a predictor for the development of aging-associated neurodegenerative diseases and aging is a risk factor for the development of Alzheimer's, Parkinson's and Huntington's diseases (Buchman et al., 2005; James et al., 2014; Liot et al., 2017). As mentioned before, during aging microglia become less neuroprotective, less effective in maintaining neuronal homeostasis and less capable of counteracting neurodegenerative alterations than young microglia (Cornejo and von Bernhardi, 2016; Cho et al., 2015; Matt and Johnson, 2016). As ghrelin, leptin, insulin, gonadal hormones and IGF-1 are neuroprotective factors and exert anti-inflammatory actions, the aging-associated decrease in their plasma levels and the increased leptin, insulin and IGF-1 resistance could contribute to the onset and propagation of the pathological alterations in the brain of patients with neurodegeneration. Obesity during midlife has also been linked to the development of age-associated neurodegenerative diseases (Procaccini et al., 2016; Spielman et al., 2014). This is probably due, at least in part, to the obesity-induced resistance to neuroprotective hormones, such as insulin, IGF-1 and leptin, and the obesity-associated activation of hypothalamic inflammatory mechanisms (Spielman et al., 2014). Therefore, hypothalamic microglial dysfunction in midlife and the consequent alteration in neuroendocrine control may represent a risk factor for the development of aging-associated neurodegeneration, with poor dietary intake and obesity possibly accelerating this process.

4. Neurodegenerative diseases accelerate hypothalamic dysfunction and loss of neuroendocrine control

4.1. Neurodegenerative diseases and hypothalamic alteration

It has been proposed that the aging-associated loss of neuroprotective properties of microglia precedes and participates in the onset of neurodegenerative alterations (Streit et al., 2009). Dysfunctional microglia in the aged brain would also contribute to the amplification of the pathological alterations that occur during the course of the disease. In turn, neurodegenerative alterations further impair microglia function (Davies et al., 2016). Aging-associated neurodegenerative diseases are usually diagnosed due to their motor and/or cognitive symptoms; however, these neurodegenerative diseases also affect systemic homeostasis. Although most studies on the pathological alterations in the brain of Alzheimer's patients have focused on cognitive brain regions such as the cerebral cortex and the hippocampus, the hypothalamus is also affected by this disease. Loss of specific hypothalamic neuronal populations and modifications in their dendritic arbors, dendritic spines

and axons have been described in patients with Alzheimer's disease and in animal models of this disease (Baloyannis et al., 2015). β -amyloid plaques and neurofibrillary tangles are also detected in the hypothalamus of Alzheimer's disease patients (Airaksinen et al., 1991) and neuroimaging techniques have revealed hypothalamic atrophy and reduced hypothalamic glucose metabolism in this neurodegenerative disease (Ishii and Iadecola, 2015).

Decreased hypothalamic volume is also detected in Parkinson's disease patients (Breen et al., 2016), together with loss of hypothalamic oxytocin, dopaminergic and orexin neurons (Fronczek et al., 2007; Politis et al., 2008b; Purba et al., 1994; Thannickal et al., 2007). Nuclear inclusion bodies with mutated huntingtin, hypothalamic atrophy and loss of specific neuropeptidergic neuronal populations, such as oxytocin, vasopressin, orexin and NPY neurons, are detected in the hypothalamus of Huntington's disease patients (Aziz et al., 2008a; Gabery et al., 2010; Kremer et al., 1990; Petersen et al., 2005; Sonesson et al., 2010; van Wamelen et al., 2013).

Pathological alterations of the hypothalamus in neurodegenerative diseases are associated with modifications in the hypothalamic control of neuroendocrine function. Indeed, modifications in plasma levels of different hormones are detected in patients with neurodegenerative diseases. For instance, male patients with Parkinson's disease have increased prolactin levels and decreased gonadal hormone levels compared to aged-matched control subjects (Nitkowska et al., 2015); LH levels are increased and free testosterone levels are decreased in male patients with Alzheimer's disease (Butchart et al., 2013), while in male patients with Huntington's disease lower testosterone and LH levels compared to aged-matched controls have been reported (Markianos et al., 2005). Furthermore, GH, ghrelin and prolactin levels are increased and IGF-1 and leptin levels are decreased in Huntington's disease patients of both sexes (Mochel et al., 2007; Popovic et al., 2004; Wang et al., 2014). High basal cortisol levels and insensitivity to glucocorticoid feedback are also observed in Alzheimer's patients, indicating impairment of hypothalamic–pituitary–adrenal axis function (Hatzinger et al., 1995; Huang et al., 2009). Hypothalamic modifications in Alzheimer's disease have also been associated with the increased bone loss observed in these patients (Loskutova et al., 2019). These endocrine alterations are indicative of a disruption in the cross-talk between the hypothalamus and the endocrine glands.

Another common characteristic of patients with advanced Alzheimer's, Parkinson's or Huntington's disease is a dramatic loss of body weight (Aziz et al., 2008b, c). This is most likely the consequence of the pathological changes in the hypothalamus of these patients. In particular, hypothalamic microglia dysfunction in these pathologies (Bisht et al., 2016; Bryan et al., 2008; Politis et al., 2008a) may contribute to accelerate the aging-associated loss of hypothalamic metabolic control by modifying the ability of astrocytes and tanycytes to sense and transport metabolic hormones and by altering the function of the blood brain barrier, which is affected in neurodegenerative diseases (Chakraborty et al., 2017). In addition, the impaired neuroprotective function of microglia in neurodegenerative diseases in the aged brain (Cornejo and von Bernhardi, 2016) could contribute to the loss of hypothalamic neurons involved in metabolic control, such as orexin and NPY neurons (Fronczek et al., 2007; Gabery et al., 2010; Petersen et al., 2005; Thannickal et al., 2007; van Wamelen et al., 2013).

4.2. Neuroprotective hormones, aging and neurodegenerative diseases

Changes in cognitive function during aging have been associated with modifications in circulating levels of neuroprotective hormones, although some conclusions are controversial. Paulsen and colleagues analyzed approximately 2000 aging subjects with no cognitive impairment at baseline to determine their 5-year risk of impaired cognitive function or dementia (Paulsen et al., 2019). They report that in men risk of developing cognitive impairment was decreased with increased IGF-1 levels, while in both men and women low levels of BDNF

were associated with increased risk of cognitive function impairment at 5 years.

Circulating IGF-1 levels in patients with Alzheimer's disease have been reported to be increased, decreased or unchanged with meta-analysis of 9 different studies indicating that no direct relationship between IGF-1 levels and Alzheimer's disease can be drawn (Ostrowski et al., 2016). However, as many factors must be taken into consideration, such as age, nutritional status, etc, the control population used for comparison is clearly important. Moreover, most studies have analyzed total circulating IGF-1 levels, while free or bioactive IGF-1 levels may be a more appropriate measurement to determine relationships with disease processes. Indeed, free IGF-1 is reported to be reduced in serum of subjects with Alzheimer's disease (Alvarez et al., 2007), with this decrease shown to be positively correlated with a significant increase in circulating TNF- α levels (Alvarez et al., 2007).

Free testosterone levels have been associated with amyloid-B levels, as well as neurodegeneration in the hippocampus, in subjects with impaired cognition, with levels of this sex steroid being positively correlated with hippocampal volume in males and inversely related with amyloid-B levels in females (Lee et al., 2017). As mentioned above, free testosterone levels are decreased in male patients with Alzheimer's disease (Butchart et al., 2013), as well as with Huntington's disease (Markianos et al., 2005).

In women, the incidence of Alzheimer's disease is reported to increase during the postmenopausal period due to the decline in neuroprotective estrogens (Depypere et al., 2016). However, estrogen treatment of postmenopausal women to decreased dementia/Alzheimer's remains controversial (Depypere et al., 2016). Estrogen treatment of recently postmenopausal women is reported to decrease amyloid- β deposition (Kantarci et al., 2016). In a nationwide case control study, postmenopausal hormone replacement was not found to be a determinant of risk for Alzheimer's disease (Imtiaz et al., 2017). In addition, in a recent study analyzing over 84,000 women diagnosed with Alzheimer's disease the long-term use of systemic steroid replacement was associated with an increased risk for this disease (Savolainen-Peltonen et al., 2019). Thus, although the lack of estrogens appears to be clearly associated with cognitive deterioration, there is no evident effect of hormonal replacement on development of Alzheimer's disease. Hormonal therapy is generally instituted once the endocrine effects of aging are apparent. As the aging process is gradual, it is possibly too late to interrupt the vicious cycle of deterioration of the endocrine axes, microglial dysfunction and neurodegeneration.

4.3. Alzheimer's disease, microglia and metabolic hormones

Changes in the hypothalamic signaling of neuroprotective hormones, which also regulate the inflammatory responses of microglia and astrocytes, will further accelerate hypothalamic dysfunction in neurodegenerative diseases. For instance, plasma leptin levels, adjusted for body weight, are reduced in Alzheimer's disease patients and in patients with age-associated dementia (Johnston et al., 2014; Witte et al., 2016). In addition, leptin transport through the blood brain barrier is impaired in animal models of Alzheimer's disease (Dietrich et al., 2008). Leptin exerts neuroprotective actions, stimulating the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways, decreasing neuroinflammation, β -amyloid levels and Tau hyperphosphorylation and preventing neuronal loss (Marwarha et al., 2014). Therefore, decreased leptin signaling may contribute to hippocampal and hypothalamic neurodegeneration in Alzheimer's disease.

Other relevant metabolic hormones in Alzheimer's disease are insulin and IGF-1. There is evidence that insulin resistance and the deregulation of glucose metabolism may contribute to enhance Alzheimer's pathology in humans (Arrieta-Cruz and Gutierrez-Juarez, 2016). Insulin signaling is decreased in the hypothalamus of mouse

models of Alzheimer's disease (Ruiz et al., 2016). IGF-1 transport to the brain is also decreased in Alzheimer's disease patients and in animal models of this disease (Trueba-Saiz et al., 2013). Impaired insulin and IGF-1 signaling in Alzheimer's disease may contribute to hypothalamic dysfunction, since both hormones activate the PI3K/Akt neuroprotective signaling pathway, which inhibits glycogen synthase kinase β (GSK3 β) and reduces Tau phosphorylation and Alzheimer's pathology. In turn, Alzheimer's pathology in the hypothalamus increases NF κ B activation (Clarke et al., 2015), which would contribute to POMC neuronal dysfunction, further promoting suppression of food intake and enhanced energy expenditure. Therefore, neurodegenerative diseases accelerate aging-associated hypothalamic dysfunction, resulting in an accelerated loss of neuroendocrine control.

4.4. Parkinson's disease, microglia and metabolism

The role of glial cells in Parkinson's disease has received increasing attention in the past decade and has been recently reviewed (Tremblay et al., 2019). One of the primary features of this neurodegenerative disease is the accumulation of proteins resulting in cell stress and eventually neuronal loss. When damaged cells are not removed the system becomes further stress, augmenting and spreading tissue damage. Although glial cells respond to local insults by producing cytokines and other factors, they are also fundamental for phagocytosis and synaptic pruning. Thus, impairment of the ability of glial cells, and particularly of microglia, to adequately remove damaged cells and debris increases neuronal stress and neuronal death.

The impairment of microglial function with aging and their reduced ability to clear away damaged cells could contribute to augment the susceptibility for neuronal loss in Parkinson's disease. Mediterranean diet, and particularly the increased intake of antioxidant phenols, is suggested to protect against the development of neurodegenerative diseases (Hornedo-Ortega et al., 2018). These dietary antioxidant effects could be executed directly at the level of the central nervous system, but also through improvement in systemic metabolism, as has been shown to occur with adherence to a Mediterranean diet (Estruch et al., 2018). Thus, once again, a general improvement in dietary habits and metabolic function can improve microglial function, decrease neuroinflammation and have beneficial effects against neurodegenerative diseases (Estruch et al., 2018; Hornedo-Ortega et al., 2018; Johnson et al., 2019).

5. Conclusions and perspectives for the future

In this review we have focused on the role of microglia in the initiation and propagation of hypothalamic dysfunction during aging and in age-associated neurodegenerative diseases (Fig. 4). A key molecule in this process is NF κ B. The uncontrolled activation of NF κ B signaling by microglia, and the resulting alterations in other glial cell types and neurons, impairs hypothalamic regulation of hormonal secretion, as well as the hypothalamic ability to sense and respond to the hormonal feed-back received from the endocrine glands. This creates a vicious circle in which the aging-associated decrease in anti-inflammatory and neuroprotective hormone levels and their hypothalamic signaling further impairs microglia and hypothalamic function, generating a cascade of events resulting in the inability of this brain center to properly control body homeostasis. This vicious circle is exacerbated under the course of neurodegenerative diseases, which affect hypothalamic function. Further studies are necessary to determine the consequences of impaired hypothalamic neuroendocrine control on the course of neurodegenerative diseases and its impact on cognitive and motor function, as well as possible mitigation of the aging and neurodegenerative processes by improved dietary habits. Moreover, neuroendocrine systems, particularly those involved in reproduction, differ between males and females, resulting in an aging process that is sex specific. This fact most likely underlies sex differences in the propensity

towards some neurodegenerative diseases during aging, as well as the susceptibility to metabolic disorders and the perpetuation of the vicious cycle of aging and indicates that studies aimed at developing effective treatments for these conditions must take sex differences into account. Although we have focused on age-associated neurodegenerative diseases in this review, it will be important to investigate the role of hypothalamic dysfunction in other neurodegenerative diseases that are accompanied by a marked loss of neuroendocrine and metabolic control, such as amyotrophic lateral sclerosis. Finally, future studies should also explore potential therapeutic interventions aimed to improve the function of microglia and to control NF κ B signaling in order to prevent or counteract the decline in neuroendocrine control with aging and disease.

Declaration of Competing Interest

The authors declare no competing financial interests.

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Appendix A. The Peer Review Overview

The Peer Review Overview associated with this article can be found in the online version, at doi:<https://doi.org/10.1016/j.pneurobio.2019.101720>.

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